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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROARK, JESSICA H	

ART UNIT	PAPER NUMBER
1644	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/892,287	Applicant(s) HILLMAN ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003 and 06 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *11 and 30-45* is/are pending in the application.

4a) Of the above claim(s) *30,33,35,44 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,31,32,34 and 36-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendments, filed 3/24/03 and 6/6/03 (Paper Nos. 13 and 15), are acknowledged.
Claims 1-10, 12-29 and 46-47 have been cancelled previously.
Claims 11, 34, 36 and 39 have been amended (it is noted claim 11 has been twice amended).
Claims 11 and 30-45 are pending.

Claims 30, 33, 35 and 44-45 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in Paper No. 7.

In view of the rejections set forth below, the issue of rejoinder of claims 30, 33, 35 and 44-45 is held in abeyance.

Claims 30, 33, 35 and 44-45 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 11, 31-32, 34 and 36-43 *are under consideration in the instant application.*

2. Sequence compliance: The CRF, paper copy of the Sequence Listing and Statement that the CRF and Sequence Listing are identical, filed 3/24/03, has been found acceptable and entered.

3. This Office Action will be in response to applicant's arguments, filed 3/24/03 and 6/6/03 (Paper Nos. 13 and 15).
The rejections of record can be found in the previous Office Action (Paper No. 12).

It is noted that New Grounds of Rejection are set forth herein. Accordingly, this Office Action is non-final.

Specification

4. Applicant's amendment, filed 3/24/03, has obviated the previous objections to the specification regarding the sequences and the lack of antecedent basis for claims 36 and 39.

Claim Objections

5. Applicant's amendment, filed 3/24/03, has obviated the previous objection to claim 34 to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim Rejections - 35 USC § 112 second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

There is a lack of antecedent basis for the recitation in claim 31 of the limitations "chimeric antibody" and "humanized antibody" because claim 11, from which claim 31 depends limits the nature of the antibody to a "human" antibody. Chimeric and humanized antibodies have components that are derived from non-human species, therefore a human antibody does not provide sufficient antecedent basis for these terms and thus it is ambiguous as to the nature of the antibodies that are encompassed by the claim.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 112 first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 11, 31-32, 34 and 36-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The claims recite as part of the invention an antibody to a polypeptide comprising "a naturally-occurring amino acid sequence having at least 90% sequence identity to SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity".

The amino acid sequence of SEQ ID NO:1 is adequately described in the specification as-filed since the structure of SEQ ID NO:1 is fully defined. Considering the art-recognized methods of making antibodies to proteins for which the amino acid sequence is defined, and the well defined structural characteristics of antibodies; the disclosure describes the genus of antibodies to SEQ ID NO:1 in sufficient detail such that the artisan can reasonably conclude that Applicant had possession of the genus of antibodies to the polypeptide of SEQ ID NO:1.

However, the instant claims are drawn to a genus of antibodies much more extensive than the genus of antibodies to the polypeptide of SEQ ID NO:1. The instant claims encompasses *any* antibody which binds *any* member of a genus of naturally-occurring polypeptides related to SEQ ID NO:1 by 90% or more amino acid sequence identity, so long as the polypeptide has phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

The language of the instant claims does provides some correlation between the structure and function of the variant polypeptides (at least 90% sequence identity relative to SEQ ID NO:1 and shared phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity).

However, the instant claims are drawn to a genus of antibodies, not to the polypeptides. Applicant does not appear to have disclosed the relevant, identifying characteristics shared by the polypeptide of SEQ ID NO:1 and sequence variants thereof necessary for antibody binding to the members of the genus of variant polypeptides (i.e., Applicant has not defined an antibody epitope).

Antibodies bind to epitopes within polypeptide structures, not to the polypeptide per se.

The Illustrated Dictionary of Immunology (1995, CRC Press, Inc. Boca Raton FL; JM Cruse and RE Lewis eds.) provides definitions of key terms regarding the binding of a polypeptide by an antibody. In particular, an "antibody-binding site" (p.19, ibid) is defined as the antigen-binding site of an antibody .... which represents the site of attachment of an epitope to the antibody molecule. The definition of an "antibody" (pp 18-19, ibid) includes the statement that [an antibody] "reacts specifically and selectively with the antigen determinants or epitopes eliciting their production or with an antigenic determinant closely related to the homologous antigen." An "antigenic determinant" (pp 22-23, ibid) is the "site on an antigen molecule that is termed an epitope and interacts with the specific antigen-binding site in the variable region of an antibody molecule known as a paratope. [ ] A lone antigen molecule may have several different epitopes available for reaction with antibody or T cell receptors." Note that in each of these definitions, the binding of antibody is recognized to be with an epitope/antigenic determinant on a molecule, not with the entire molecule (e.g., see the illustration of an antigenic determinant on page 23, ibid). In defining an "epitope" (pp 102-103), the Illustrated Dictionary of Immunology notes that an "epitope" is "an antigenic determinant", that "[i]t must be at least 1kD to elicit an antibody response" and that "[m]ultiple epitopes may be found on large nonpolymeric molecules".

Van Regenmortel (Methods: A Companion to Methods in Enzymology, 1996; 9:465-472) provides a more in-depth consideration of the binding of an antibody to its epitope contained within a larger protein/polypeptide structure (see entire document). In particular, Van Regenmortel discusses that an antibody's epitope in structural terms is only 15-22 residues of the protein (see especially page 466, right column, and the illustration of the three dimensional structure of epitopes on one well-characterized protein in Figure 1 on page 468).

Thus adequate identification of one or more epitopes shared by members of a genus of variant polypeptide structures is essential to describing a distinguishing identifying characteristic sufficient to show that Applicant was in possession of the claimed genus of antibodies. Thus when the claims are not limited to either a defined polypeptide sequence, or to polypeptides encompassing sequence variation but sharing a *defined* antibody epitope, the ordinary artisan would not conclude that there was sufficient structural constraints placed upon the antibody now claimed to show that Applicant was in possession of the genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. Claims 11, 31-32, 34 and 36-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies in various forms which bind SEQ ID NO:1, does not reasonably provide enablement for antibodies which bind a polypeptide comprising "a naturally-occurring amino acid sequence having at least 90% sequence identity to SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's arguments, filed 3/24/03 and 6/6/03 regarding the reintroduction of the percent identity limitation, have been fully considered in view of the amended claims but have not been found convincing.

Applicant's arguments are addressed below.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, unpredictability in the art, the amount of experimentation required, and the amount of direction or guidance presented.

Applicant has disclosed antibodies to the polypeptide of SEQ ID NO:1, which is the ordinary artisan would consider more likely than not to be a phosphatidylinositol 4,5-bisphosphate 5-phosphatase.

However, the specification does not appear to disclose any other naturally-occurring polypeptides at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity. Neither does the specification appear to disclose which sequences of the polypeptide of SEQ ID NO:1 are essential for phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity.

The specification does not appear to be sufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. Despite knowledge in the art for producing antibodies to specific sequences, the specification fails to provide guidance regarding which polypeptide variant retains the instantly recited phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity. Furthermore, it is not routine in the art to screen large numbers of encoded amino acid variants where the expectation of retaining similar function is unpredictable based on the instant disclosure.

Applicant argues that that specification does provide sufficient guidance as to how to identify naturally-occurring variants, e.g., on page 48, and concludes that given the skill in the art the experimentation required to identify these naturally-occurring variants would not be undue. Applicant points to In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971) for support that nothing more than objective enablement need be provided.

However, even though the level of skill in the art for isolating "naturally-occurring" polypeptides encoded by nucleic acids related to the nucleic acid encoding SEQ ID NO:1 may have been high with respect to the techniques employed, skill in the art does not render the existence of a "naturally-occurring" polypeptide predictable.

Consequently, a person of skill in the art is not enabled to make and use an antibody to a "naturally-occurring" polypeptide at least 90% identical to SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity; as encompassed by the full breadth of the claims as currently recited, irrespective of the particular form or species of origin of the antibody, because it is unpredictable that other naturally-occurring polypeptides having the recited sequence identity and activity existed in view of the limited guidance in the specification as filed and the single working example.

In addition, the instant claims are not drawn to the polypeptide, but rather to a genus of antibodies which bind any member of the genus of polypeptides. The specification discloses a single species of polypeptide that is a naturally-occurring amino acid sequence having at least 90% sequence identity to the sequence set forth in SEQ ID NO: 1; the amino acid sequence of SEQ ID NO:1 itself.

The instantly recited genus encompasses antibodies to polypeptides having differences in linear and conformational epitopes necessary for antibody recognition. However, the specification fails to provide sufficient guidance as to the antibody epitopes in SEQ ID NO:1, either linear or conformational, that results in antibodies that bind the polypeptide of SEQ ID NO:1. Definition of the epitope(s) of a particular polypeptide recognized by an antibody is essential to both make and use an antibody to variants of the polypeptide of interest. Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444, of record) teaches single amino acid substitutions **outside** the antigenic site on a protein effect antibody binding; thus it is also essential to provide some guidance as to the identity of the flanking sequences of a fragment of a polypeptide of interest. Further, Li et al. (Proc. Natl. Acad. Sci. USA 77: 3211-3214, 1980, of record) disclose the dissociation of immunoreactive from other biological activities when constructing analogs (see entire document).

Further, the uses set forth for antibodies in the specification require that the antibody bind the polypeptide of SEQ ID NO:1. Unless the claimed antibody binds the disclosed polypeptide, the skilled artisan clearly would not know how to use that antibody in view of the guidance provided in the specification.

Thus in the absence of guidance to a particular epitope and the structural context in which the epitope is found; it is highly unpredictable which other isolated polypeptides comprising a variant sequence of SEQ ID NO:1 would maintain the relevant antibody epitope(s).

The scope of the claimed antibodies is not commensurate with the enablement provided by the disclosure with regard to the various isolated polypeptides comprising variant sequences as broadly encompassed by the claimed invention. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without further guidance as to the nature of the antibody epitope and as to whether other naturally-occurring variants even existed; it would require undue experimentation to make and use antibodies to variants of the polypeptide of SEQ ID NO:1.

Consequently, the Examine maintains that the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claim Rejections – 35 U.S.C. § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. For examination purposes, the rejections set forth below are with respect to the enabled embodiments of the invention, i.e., those antibodies which bind a polypeptide having *the* amino acid sequence set forth in SEQ ID NO:1.

13. Applicant's amendment, filed 3/24/03 and limiting claim 11 to a human antibody, has obviated the rejection of record of claims 11, 32 and 34 under 35 U.S.C. 103(a) as being unpatentable over Laxminarayan et al. (J. Biol. Chem. 1993; 268:4968-4974, of record) in view of GenBank Accession #AAB03214 (Nussbaum, R.L., (GI 1399101, GenBank Sequence Database, Accession No. AAB03214, National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD 20894, Release Date 29 June 1996, Version AAB03214.1, of record), as evidenced by the alignment previously provided.

14. Applicant's amendment, filed 3/24/03 and limiting claim 11 to a human antibody, has obviated the rejection of record of claims 11, 32 and 34 under 35 U.S.C. 103(a) as being unpatentable over Palmer et al. (J. Biol. Chem. 1994; 269(5):3403-3410, of record) in view of GenBank Accession #AAB03214 (Nussbaum, R.L., (GI 1399101, GenBank Sequence Database, Accession No. AAB03214, National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD 20894, Release Date 29 June 1996, Version AAB03214.1, of record), as evidenced by the previously provided alignment.

15. Claims 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laxminarayan et al. (J. Biol. Chem. 1993; 268:4968-4974, of record) in view of GenBank Accession #AAB03214 (Nussbaum, R.L., (GI 1399101, GenBank Sequence Database, Accession No. AAB03214, National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD 20894, Release Date 29 June 1996, Version AAB03214.1, of record), as evidenced by the alignment previously provided.

The claims are drawn to polyclonal antibodies which specifically bind a polypeptide comprising the amino acid sequence of SEQ ID NO:1, or a polypeptide comprising a naturally occurring sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity, as well as to methods of making said antibodies by immunizing an animal with a polypeptide *having an* amino acid sequence of SEQ ID NO:1.

Applicant's arguments, filed 3/24/03 and 6/6/03, have been fully considered in view of the amended claims but have not been found convincing.

The rejection of record may be found in Paper No. 12 at Section 14 and is incorporated herein as if reiterated in full.

Applicant argues that the claims as amended are limited to human antibodies in view of the amendment to claim 11 to recite this limitation. As noted supra, this particular rejection of record with respect to amended claim 11 is acknowledged to have been obviated by Applicant's amendment to limit claim 11 to human antibodies.

However, claims 36-38 are not limited to human antibodies. Instead, claim 36 requires only that the polyclonal antibody have "the specificity of the antibody of claim 11". For the reason of record in Paper No. 12 at Section 14, the teaching of the combination of the references provides sufficient motivation and reasonable expectation of success for the ordinary artisan at the time the invention was made to produce a polyclonal antibody with the specificity of the antibody of claim 11. Species of origin has no bearing on the specificity of the antibody.

Applicant also argues that the phrase "specifically bind" excludes antibodies which bind sequences having even one amino acid residue different from SEQ ID NO:1 or a naturally-occurring amino acid sequence at least 90% identical to SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity. Applicant argues that the skilled artisan is able to make antibodies which do not cross-react between closely related amino acid sequences.

The Examiner acknowledges that is possible to *select* for antibodies which bind a protein of interest but do not bind a closely related protein. However, selection of the subset of antibodies with the property of binding one protein but not a closely related protein requires a screening strategy that is neither taught in the specification as filed, nor claimed. "Specific binding", contrary to Applicant's assertions, does not limit the binding of the antibody to a single protein, but rather to a single epitope. It is again noted that arguing that "specific binding" excludes binding of related proteins which share epitopes with the protein of interest argues limitations that not only are not claimed, but that are contrary to both the art-recognized usage of the term "specific binding", and the usage of the term in the specification as filed..

Finally, it is noted that although claim 36 has been amended and now recites immunization with a polypeptide having an amino acid sequence of SEQ ID NO:1, the phrase "having an amino acid sequence" reads on subsequences of SEQ ID NO:1 (as opposed to "having the amino acid sequence", which would require immunization with a polypeptide comprising the full length sequence set forth in SEQ ID NO:1. As set forth in the rejection of record, the polypeptide of AAB03214 comprises numerous subsequences of SEQ ID NO:1. Therefore, immunizing with the polypeptide of AAB03214 meets the limitation of method claim 36 as to the polypeptide used to immunize.

Therefore, the Examiner maintains that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection of record is therefore maintained because the amendment does not obviated the basis of the rejection.

16. Claims 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palmer et al. (J. Biol. Chem. 1994; 269(5):3403-3410, of record) in view of GenBank Accession #AAB03214 (Nussbaum, R.L., (GI 1399101, GenBank Sequence Database, Accession No. AAB03214, National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD 20894, Release Date 29 June 1996, Version AAB03214.1, of record), as evidenced by the previously provided alignment.

The claims are drawn to monoclonal antibodies which specifically bind a polypeptide comprising the amino acid sequence of SEQ ID NO:1, or a polypeptide comprising a naturally occurring sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity, as well as to methods of making said antibodies by immunizing an animal with a polypeptide *having an* amino acid sequence of SEQ ID NO:1.

Applicant's arguments, filed 3/24/03 and 6/6/03, have been fully considered in view of the amended claims but have not been found convincing.

The rejection of record may be found in Paper No. 12 at Section 15 and is incorporated herein as if reiterated in full.

Applicant's arguments regarding the inclusion of "human" in claim 11 have been addressed supra, as have the comments regarding "specific binding".

Regarding the Palmer reference, Applicant also argues that because Palmer et al. teach bovine, rather than human, antibodies, Palmer et al. actually teach away from human antibodies.

As noted supra, the claims are not limited to human antibodies. In addition, it is noted that the species used by Palmer et al. to produce antibodies is mouse (BALB/c), not bovine (see page 3404 "Preparation of monoclonal antibodies").

Therefore, the Examiner maintains that the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection of record is therefore maintained because the amendment does not obviated the basis of the rejection.

17. Claims 11, 31-32, 34 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palmer et al. (J. Biol. Chem. 1994; 269(5):3403-3410, of record) in view of GenBank Accession #AAB03214 (Nussbaum, R.L., (GI 1399101, GenBank Sequence Database, Accession No. AAB03214, National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD 20894, Release Date 29 June 1996, Version AAB03214.1, of record), as evidenced by the alignment provided previously, and as evidenced by Bost et al. (Immunol. Invest. 1988; 17:577-586) and Bendayan (J. Histochem. Cytochem. 1995; 43:881-886), and further in view of Ramakrishnan et al. (US Pat. No. 5,817,310, of record).

The amended claims are drawn to a *human* antibody, or various forms of a human antibody, which specifically bind a polypeptide comprising the amino acid sequence of SEQ ID NO:1, or a polypeptide comprising a naturally occurring sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity, and to antibodies produced by screening recombinant immunoglobulin and Fab expression libraries.

Applicant's arguments, filed 3/24/03 and 6/6/03, have been fully considered in view of the amended claims but have not been found convincing. Applicant's arguments have been addressed above, but will be addressed herein in the context of the application of the rejection of record to the amended claims.

As previously noted, Palmer et al. teach the purification and characterization of two phosphatidylinositol 4,5-bisphosphate 5-phosphatases found in bovine brain cytosol (see entire document, e.g., Abstract). Palmer et al. teach the production of monoclonal antibodies to components of a partially purified preparation having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity, and further teach that monoclonal antibodies to phosphatidylinositol 4,5-bisphosphate 5-phosphatases are useful tools to study the distribution, structure, and regulation of these two forms of phosphatidylinositol 4,5-bisphosphate 5-phosphatases (see entire document, as summarized in Abstract)

Palmer et al. teach compositions comprising the monoclonal antibodies and a suitable carrier that is an acceptable excipient, since the monoclonal antibodies in ascites fluid is taught (e.g., page 3404, "Preparation of Monoclonal Antibodies") and the monoclonal antibody in glycine is taught (e.g., page 3404 "Two-antibody Sandwich Assays").

Palmer et al. also teach labeling the monoclonal antibodies with biotin (e.g., page 3404 "Two-antibody Sandwich Assays" and Table III).

Palmer et al. teach the application of the monoclonal antibodies in a variety of assays for characterization of the phosphatidylinositol 4,5-bisphosphate 5-phosphatase, including immunoprecipitation, western blotting and ELISA (see entire document, especially page 3404, "Experimental Procedures" and Figures 5-7 and Table II and III).

Palmer et al. teach methods of making monoclonal antibodies by immunizing an animal with the partially purified enzyme, isolating spleen cells which includes the antibody-producing cells, fusing the spleen cells with an immortalized cell line to produce hybridomas, culturing the hybridomas and isolating from the hybridoma culture monoclonal antibodies (see page 3404, especially "Preparation of Monoclonal Antibodies").

As previously acknowledged, Palmer et al. differ from the instant claims in that the phosphatidylinositol 4,5-bisphosphate 5-phosphatases is not a polypeptide comprising the amino acid sequence of SEQ ID NO:1, or a polypeptide comprising a naturally occurring sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity.

In addition, Palmer et al. do not teach the production of human antibodies, as recited in the amended claims.

As previously noted, GenBank Accession #AAB03214 teaches a protein sequence that is a phosphatidylinositol (4,5)bisphosphate 5-phosphatase homolog.

The protein of GenBank Accession #AAB03214 from position 2 to position 329 is 99.4% identical to the polypeptide of SEQ ID NO:1 from position 45 to position 372, as evidenced by the alignment previously provided.

Thus the protein taught by GenBank Accession #AAB03214 is a polypeptide comprising a naturally occurring sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity.

Although the protein of GenBank Accession #AAB03214 lacks amino acids 1-44 of SEQ ID NO:1, the ordinary artisan at the time the invention was made would have found it obvious to produce monoclonal antibodies to the protein of GenBank Accession #AAB03214 using the methods taught by Palmer et al. The ordinary artisan would have been motivated to produce monoclonal antibodies to the amino acid sequence set forth in GenBank Accession #AAB03214 in order to isolate this protein, characterize this new phosphatidylinositol 4,5-bisphosphate 5-phosphatase, and compare it to other phosphatidylinositol 4,5-bisphosphate 5-phosphatase for which the molecular identity was not yet known. Alternatively, the ordinary artisan at the time the invention was made would have been motivated to produce antibodies to GenBank Accession #AAB03214 in order to characterize the cell type expression and subcellular localization of this phosphatidylinositol 4,5-bisphosphate 5-phosphatase.

As taught by Palmer et al., at the time the invention was made, characterization of phosphatidylinositol 4,5-bisphosphate 5-phosphatases using monoclonal antibodies was well known in the art and the ordinary artisan had a reasonable expectation of successfully producing monoclonal antibodies to any phosphatidylinositol 4,5-bisphosphate 5-phosphatase for which at least a partially purified preparation could be obtained.

Given the extensive homology between GenBank Accession #AAB03214 and the polypeptide of SEQ ID NO:1, any antibody produced to the 5-phosphatase of GenBank Accession #AAB03214 would necessarily specifically bind to each of a polypeptide comprising both a naturally occurring sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity, and a polypeptide having *the* amino acid sequence of SEQ ID NO:1.

Applicant argues that the phrase "specifically bind" excludes antibodies which bind sequences having even one amino acid residue different from SEQ ID NO:1 or a naturally-occurring amino acid sequence at least 90% identical to SEQ ID NO:1 and having phosphatidylinositol 4,5-bisphosphate 5-phosphatase activity. Applicant argues that the skilled artisan is able to make antibodies which do not cross-react between closely related amino acid sequences.

The Examiner again acknowledges that is possible to select for antibodies which bind a protein of interest but do not bind a closely related protein. However, selection of the subset of antibodies with the property of binding one protein but not a closely related protein requires a screening strategy that is neither taught in the specification as filed, nor claimed. "Specific binding", contrary to Applicant's assertions, does not limit the binding of the antibody to a single protein, but rather to a single epitope. It is again noted that arguing that "specific binding" excludes binding of related proteins which share epitopes with the protein of interest argues limitations that not only are not claimed, but that are contrary to both the art-recognized usage of the term "specific binding", and the usage of the term in the specification as filed.

For example, Bost et al. describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies which bound either the HIV or IL-2 derived sequence did not cross react with irrelevant peptides (e.g., "Results, page 579).

Similarly, Bendayan characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin and shows that although the antibody is highly specific; it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagon, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph).

Palmer et al. in view of GenBank Accession #AAB03214 differ by not teaching that the monoclonal antibodies are human antibodies which bind the human polypeptide, by not teaching single chain or Fab/F(ab')$_2$ fragments of the human antibody, nor by teaching that human antibodies can be isolated from Fab expression and recombinant immunoglobulin libraries.

However, one of ordinary skill in the art at the time the invention was made recognized that there were many ways to produce an antibody, and that antibodies produced from different species (e.g., human versus mouse) and in different forms (e.g., Fab versus single chain) were art-recognized interchangeable variants of one another, any of which could be used in methods of characterizing the protein of interest. Human antibodies were also well known in the art to be highly desirable because they could be used for not only detection and diagnostic assays, but also could be administered in vivo if desired.

For example, Ramakrishnan et al. teach that the ordinary artisan at the time the invention was made recognized that antibodies could be formulated in any of a variety of interchangeable forms for use as compositions comprising a pharmaceutically acceptable carrier in a variety of art recognized assays to detect a protein of interest (see entire document, especially columns 8-17). Ramakrishnan et al. teach the production of human antibodies to a protein of interest can be accomplished using any of several art-recognized methods (see columns 8-15, especially the description of EBV transformation at column 12, lines 10-37, the screening of Fab libraries at column 12, lines 56-65, and the use of transgenic mice at column 14, lines 10-25). Ramakrishnan et al. teach that it was well known in the art that antibodies to a protein of interest could produced by screening a recombinant immunoglobulin library which encode either the antibodies or fragments thereof (i.e. Fab) (e.g., see column 12 at line 56 to column 13).

Ramakrishnan et al. teach that antibodies can be single chain antibodies, Fab fragments, or F(ab')$_2$ fragments (see e.g. column 9 at lines 9-27). Further, compositions comprising antibodies in a pharmaceutically acceptable carrier, and various art recognized applications of antibodies for detection are taught in columns 15-17. Labeling of antibodies is also taught (e.g., column 11).

Therefore, it would have been obvious to the ordinary artisan at the time the invention was made to prepare human antibodies in any of the instantly recited forms for use in art-recognized assays such as those of western blotting, ELISA and immunoprecipitation as taught by Palmer et al. The ordinary artisan would have been motivated to make these various forms of human antibodies in view of the art-recognized interchangeability of the different antibody forms and in order to provide a variety of detection reagents that could be used in detection assays such as the western blotting assay taught by western blotting, ELISA and immunoprecipitation as taught by Palmer et al. The ordinary artisan recognized the advantage of antibody variants for use in such detection assays because depending upon the other antibodies used in combination, the antibody variants could be labeled using differential secondary reagents, thus avoiding high backgrounds in ELISA and immunoblotting assays.

In addition, the ordinary artisan at the time the invention was made would have been motivated to make human antibodies in particular because antibodies that were fully human provide the greatest flexibility in terms of applications for which the antibodies could be used, since human antibodies, besides being applicable to detection and other in vitro assays, could also be administered in vivo should a therapeutic application be identified. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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